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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/148,234	09/04/1998	IOANNIS MOUTSATSOS	GI5298A	3002

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EXAMINER	
LEFFERS JR, GERALD G	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/148,234	MOUTSATSOS ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a supplemental amendment, filed 3/29/2004, in which the pending claims were cancelled and new claims were added (claims 24-28). Claims 24-28 are pending and under consideration in the instant application.

Any rejection of record in the previous office actions not addressed herein is withdrawn. This action is FINAL as the new grounds of rejection recited herein were necessitated by applicants' amendment of the claims in the response filed 3/29/2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection, necessitated by applicants' amendment of the claims in the response filed 3/29/2004.**

Each of the claims is directed to a method of inducing functional bone formation at a site of bone infirmity in a human comprising a step of transforming a "mesenchymal stem cell" with a DNA encoding BMP-2. The term "mesenchymal stem cell" encompasses a broad genus of stem cells that might be used in the recited methods. However, there does not appear to be literal

support in the specification as originally filed for the term "mesenchymal stem cell", and therefore, there is no support for claiming methods that encompass the broad genus of cells embraced by the cited term. Thus, the new claims comprise impermissible NEW MATTER.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ahrens et al (DNA and Cell Biology, Volume 12, NO. 10, pages 871-880, 1993; see the entire reference) in view of Bonadio et al (U.S. Patent No. 5,763,416; see the entire patent) and Lee et al (U.S. Patent No. 6,048,964; see the entire patent). **The grounds for this rejection are maintained for reasons of record in the previous office action mailed 5/21/2003 and which are applied to the recited new claims.**

Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ahrens et al (DNA and Cell Biology, Volume 12, NO. 10, pages 871-880, 1993; see the entire reference) in view of Bonadio et al (U.S. Patent No. 5,763,416; see the entire patent) and Lee et al (U.S. Patent No. 6,048,964; see the entire patent) as applied to claims 24-26 above, and further in view of Wozney et al (U.S. Patent No. 6,291,206; see the entire patent). **The grounds for this rejection are maintained for reasons of record in the previous office action mailed 5/21/2003 and which are applied to the recited new claims.**

Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ahrens et al (DNA and Cell Biology, Volume 12, NO. 10, pages 871-880, 1993; see the entire reference) in view of Bonadio et al (U.S. Patent No. 5,763,416; see the entire patent) and Lee et al (U.S. Patent No. 6,048,964; see the entire patent), and Wozney et al (U.S. Patent No. 6,291,206; see the entire patent) as applied to claims 24-27 above, and further in view of Hattersley et al (U.S. Patent No. 5,700,774; see the entire patent). **The grounds for this rejection are maintained for reasons of record in the previous office action mailed 5/21/2003 and which are applied to the recited new claims.**

Response to Arguments

Applicant's arguments filed 3/29/2004 have been fully considered but they are not persuasive. The response filed 3/29/2004 essentially argues: 1) the combination of references do not make the invention obvious, 2) there would have been no reasonable expectation of success

in practicing methods according to the combination of references, 3) the results described by Ahrens et al are only *in vitro* results and are not predictive of success for *ex vivo* treatments, 4) the *in vitro* results taught by Ahrens et al are not predictive of autocrine and/or paracrine effects of implanted recombinant mesenchymal cells that express BMP-2, 5) success of *in vivo* gene transfer experiments or *in vitro* transformation of a stem cell with a gene encoding BMP-2 does not predicate success of implantation of ex vivo cultured cells and formation of enhanced, functional bone formation, and therefore, obtaining similarly beneficial results is not an expected and obvious outcome, 6) the Declaration provided by Dr. Gazit provides evidence that one of skill in the art would not have found it obvious to obtain the instant invention (e.g. "direct *in vivo* gene transfer is not predictive a priori for use of *ex vivo* engineered cells for implantation for bone repair, and therefore, obtaining credible and/or functional results is not *a priori* an expected and/or obvious outcome" and "it would not have been obvious that a person of ordinary skill in the art would have had a reasonable expectation of success in the producing of the instant invention given the teachings of Bonadio in combination with He, McKay and/or Hattersley."), 7) none of the cited references reduce the claimed invention to practice and thus do not provide evidence of "enhanced" bone repair as the result of autocrine and paracrine mechanisms, and 8) the unexpected results of a higher efficiency of the extent of bone regeneration and a more organized deposition along fracture edges were due to the participatory effects mediated by the autocrine and paracrine mechanisms involved.

Assertions in the response and in the declaration filed by Dr. Gazit that there would have been no expectation of success in practicing the claimed invention are not supported in a convincing manner. For example, there does not appear to be any limitation in the new claims

with regard to any *enhanced* level of functional bone formation upon *ex vivo* implantation of the cultured mesenchymal stem cells. The only limitation that comes close to any recitation of an "enhanced" level of functional bone formation is the limitation that the therapeutic effect is mediated by both autocrine and paracrine effects of the expressed BMP-2 protein. However, as was pointed out in making the rejections, Bonadio et al expect that their transplanted cells expressing osteotropic genes will function by effects on the recombinant cells themselves (i.e. autocrine effects) and effects on neighboring cells (e.g. paracrine effects; see, for example, column 4, lines 32-48; column 5, lines 1-19; columns 6-7, bridging paragraph; columns 8-9, bridging paragraph). For example, Bonadio et al teach that the "bone progenitor cells" of their invention refers to any or all of those cells that have the capacity to ultimately form, or contribute to the formation of new bone tissue (e.g. stem cells and/or genetically engineered cells; see column 4, lines 32-48). That autocrine and paracrine effects are anticipated for transformed cells of their invention is further supported by the teaching that the transformed cells of their invention include ones which express factors that are reasonably expected to affect both the cells themselves and neighboring cells (e.g. a cell expressing a BMP protein, PTH and a receptor for the BMP protein; see columns 8-9, bridging paragraph). Moreover, the teachings of Ahrens et al would lead the ordinarily skilled artisan to expect that C3H10T1/2 cells (i.e. the same cells used by applicants in their ex vivo experiments) overexpressing BMP-2 would likely undergo developmental effects due to the overexpression of BMP-2 since Ahrens et al teach that these cells form bone-like cell structures *in vitro* upon expression of BMP-2. Finally, the motivation provided by the examiner for combining the cited references does not rely necessarily upon any expectation of both autocrine and paracrine effects, merely that the cited references comprise

teachings that provide a reasonable expectation of success in treating a site of bone infirmity in a human through the use of cultured mesenchymal stem cells (i.e. the "bone progenitor cells" of Bonadio et al or the C3HT101/2 cells taught by Ahrens et al) that overexpress BMP-2. The fact that both autocrine and paracrine effects would necessarily have been present in such methods made from the combined teachings of the cited references (e.g. with the C3HT101/2 cells taught by Ahrens et al) is evidenced by applicants' own data.

With regard to the arguments concerning unexpected results and the data discussed in the declaration by Dr. Gatiz, the data presented appears to be an "apples to oranges" comparison and does not indicate that there would not have been a reasonable expectation of success in combining the teachings of the cited references to practice the claimed methods. For example, experiments are discussed where the direct administration of the BMP-2 protein is compared to expression of the protein in transplanted cells. Alternatively, an experiment is discussed that demonstrates that cells that would not normally be expected to undergo autocrine effects (i.e. CHO cells expressing BMP-2) show qualitatively and quantitatively less desirable bone formation relative to the mesenchymal stem cells of the invention. Neither of these experiments addresses the issue of unexpected results in a meaningful way with regard to the methods that are actually claimed. The recited methods, and the application of the combined teachings of the cited references, are directed to a method of treatment using transformed mesenchymal stem cells that overexpress BMP-2 and are not directed to methods of direct administration of the BMP-2 protein or implantation of CHO cells that overexpress BMP-2.

The most meaningful experiment to address the issue of unexpected results would have been a comparison of an *ex vivo* method practiced according to the combined teachings of the

cited references versus the system taught by applicants. This would have directly addressed the issue of whether the methods taught by applicants demonstrate any unexpected results relative to the methods made by the combination of the teachings of the cited references. No such discussion or evidence is provided in the declaration by Dr. Gatiz or in applicants' response. Again, based upon the combined teachings of the cited references and the level of skill in the art at the time of the invention, there would have been a reasonable expectation of success in practicing the recited methods to treat a site of bone infirmity in a human using the combined teachings of the cited references. Moreover, for the reasons outlined above, the transformed and implanted cells made according to the combined teachings of the cited references would necessarily exhibit both autocrine and paracrine effects. Therefore, the recited methods of inducing functional bone formation at a site of bone infirmity in a human remain obvious over the art of record.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1636

ggl

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PRIMARY EXAMINER